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# Febuxostat therapy in outpatients with suspected COVID-19: A clinical trial

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**#The authors confirm that the Principal Investigator for this paper is Dr. Lotfollah Davoodi and that he had direct clinical responsibility for patients.**

**Running title:** Febuxostat for patients infected with COVID-19

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**What is already known about this subject**

- Coronavirus (COVID-19)–caused respiratory tract illness may result to severe progressive pneumonia, multiorgan failure and death in critically ill patients.
- Inflammatory response and storm cytokine production are involved in pulmonary tissue damage in patient with COVID-19.
- There is no specific antiviral treatment against COVID-19 infection.

**What this study adds**

- Fever, cough and tachypnea significantly mitigated in patients with COVID-19 after febuxostat treatment, in addition, the lymphocytes count significantly increased after febuxostat treatment.
- The mean percentages of CT abnormalities were significantly reduced to 47% compared to baseline after febuxostat treatment.
- The efficacy of febuxostat and hydroxychloroquine in treatment of outpatients with COVID-19 infection was not significantly different.

**Abstract**

**Background:** The aim of this clinical trial was to evaluate the effects of febuxostat (FBX) in comparison with hydroxychloroquine (HCQ) on clinical symptoms, laboratory tests and chest CT findings in outpatients with moderate symptoms of COVID-19 infection.

**Methods:** We conducted a clinical trial involving adult outpatients with the moderate respiratory illness following COVID-19 infection. Patients were randomly assigned to receive either FBX or HCQ for 5 days. The measured variables were needs to hospitalization, clinical and laboratory data including fever, cough, breathing rate, C-Reactive Protein level, lymphocytes count at onset of admission and was well as at 5 days of treatments. In addition, CT findings were evaluated on admission and 14 days after initiation of treatment.

**Results:** Sixty subjects were enrolled in the study with a 1 to 1 ratio in FBX and HCQ groups. On admission, fever (66.7%), cough (87%), tachypnea (44.4%), dyspnea (35%), elevated CRP value (94.4%) and lung involvement according to chest CT (100%) were documented in enrolled patients with insignificant difference between FBX and HCQ groups. Fever, cough and tachypnea were significantly mitigated in both groups after five days of treatments without any significant differences between groups. The mean percentages of lung involvement were significantly reduced to 7.3% and 8% after 14 days of treatment with FBX and HCQ, respectively. In adult outpatients with moderate COVID-19 infection, the effectiveness of FBX and HCQ was not different in terms of resolution of clinical manifestations, laboratory tests and lung CT findings.

**Conclusion:** This trial suggests that FBX is as an alternative treatment to HCQ for COVID-19 infection and may be considered in patients with a contraindication or precaution to HCQ.

**Keywords:** COVID-19; febuxostat; hydroxychloroquine; inflammation; lung; pneumonia; SARS-CoV-2



## 1.INTRODUCTION

Coronavirus disease 2019 (COVID-19) causes respiratory tract illness which may result to severe progressive pneumonia, multiorgan failure and death in critically ill patients [1, 2]. There is no specific antiviral treatment against Covid-19 infection but some antiviral drugs have been used as empirical [3]. The current therapy for COVID-19 infection focuses on symptomatic treatment and supportive care. Patients with severe coronavirus disease have lower lymphocytes count, higher leukocytes count and lower percentages of monocytes, eosinophils, and basophils. Elevation in inflammatory cytokines including IL-2R, IL-6, IL-8, IL-10, and TNF-α and dysregulation of immune system has been observed [4]. The expression levels of interleukin-2 receptor (IL-2R) and serum level of IL-6 were associated with severity of disease [5]. In addition, virus infection causes nuclear factor kappa B (NF-κB) overexpression, which plays central role in massive overproduction of pro-inflammatory cytokines as well as triggering a variety of cellular responses, including cell phagocytosis, maturation of dendritic cells, and chemotaxis of cells [6]. The uncontrolled inflammatory response may result in pulmonary tissue damage, functional impairment, and reduced lung capacity. Hence, it is proposed that an excessive production of IL-6 is associated with severe lung damage and acute respiratory illness in patients with COVID-19 infection. Febuxostat (FBX) is a

novel non-purine xanthine oxidase (XO) approved for treating hyperuricemia in patients with gout. Several studies have already demonstrated the anti-inflammatory [7], anti-oxidant [8] and anti-apoptosis effects of FBX [9]. Several preclinical studies showed that FBX inhibits inflammatory responses through reducing the levels of pro-inflammatory mediators such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6 and NF-κB [10-12]. It protects animal against toxic-induced lung inflammation through downstream inflammatory mediators and oxidative stress [13-15]. FBX markedly accelerates pulmonary endothelial barrier recovery and improves survival in lipopolysaccharide-induced murine sepsis [16]. This clinical trial was conducted to assess the effects of FBX and hydroxychloroquine (HCQ) on clinical symptoms, laboratory tests and chest CT findings of patients with COVID-19 infection.

## 2.METHODS

### *2.1.Study Design*

A clinical trial was conducted on outpatients with COVID-19 infections from March 16, 2020, to April 10, 2020, at Mostafavian Fever Clinic in Sari (Iran). This study was an open label clinical trial, with blinded outcome assessment. This study was approved by the Ethical Committee (ID; IR.MAZUMS.REC.1398.7294) and Research Council of Mazandaran University of Medical Sciences and was submitted and approved by the Iranian Registry of Clinical Trials (ID; IRCT2019072704434N1, the full trial protocol can be accessed at: http://www.irct.ir). The study was performed in accordance with declaration of Helsinki. All patients signed the informed consent form. Sample size was determined 30 patients in both group based on effect size = 0.3 for difference in response rate as a primary endpoint, power = 80% and alpha = 0.05 for this study, as a two-sided superiority trial [17, 18].

### *2.2.Patients*

Inclusion criteria were as following 1; chest CT finding compatible with COVID-19 infection along with other symptoms of coronavirus infection. Bilateral and peripheral ground-glass and consolidative pulmonary opacities were the hallmarks of CT findings. 2; any symptoms of respiratory tract

involvement including cough, dyspnea or tachypnea along with a history of contact with a known case of COVID-19 3; creatinine clearance greater than 60 ml/min. The exclusion criteria include: 1; Suspicious patients for COVID-19 pneumonia who had severe underlying diseases such as cardiovascular, lung and kidney diseases, 2; patients with severe pneumonia needing hospitalization, 3; patient who were unable to take oral medications and 4; concurrent use of azathioprine, didanosine, mercaptopurine or pegloticase (due to drug interaction with FBX).

### *2.3.Interventions*

Patients were randomized using the balance block method to receive HCQ (30 patients) or FBX (30 patients). HCQ were administered one tablet of HCQ 200 mg twice daily (Amin Pharmaceutical Company, Iran). Patients in FBX group took one tablet of FBX 80 mg per day (Jalinus Pharmaceutical Company, Iran). All patients were taken acetaminophen 325 mg, as needed, for controlling the fever. The pharmaceutical companies were neither involved in the design nor in the financial support of the study. Study drugs were purchased from an official Iranian pharmacy. Amin and Jalinus pharmaceutical companies did not access to the data of the study during trial and prior publication. The treatment duration was five days. Both patients and physician did not know the contents of tables.

### *2.4.Outcome measures*

The primary outcome of this study was the rate of hospitalization. Secondary outcomes were clinical improvements (e.g., resolution of fever, cough and dyspnea) and improvement of CT findings at days 14 after initiation of the treatment. Patients were assessed clinically (e.g., temperature, respiratory rate, cough, and dyspnea) and paraclinically (e.g., CBC-diff and C-Reactive Protein) at onset of admission and 5$^{th}$ day of treatment. In addition, the chest CT scans were done at first and 14 days after the onset of treatment. For each patient, the chest CT scan was evaluated for the presence of ground-glass opacities and/or consolidation. Each five lobe of the lung was assessed and the overall lung involvement was reached by summing the five lobe scores (range of possible scores, 0 – 20 for each lobe and total lung involvement of possible score of 0-100 percent). The Chest CT was repeated in day 14 and compared with the initial finding. Reduced lung CT involvement; not adjusted" values were computed according to this equation:

Reduced Lung CT involvement, not adjusted =

Day 14 total long involvement – Initial total lung involvement

Reduced lung CT involvement; adjusted values was computed with the following equation that included the initial total lung involvement in the denominator:

Reduced lung CT involvement; adjusted value =

$$\frac{(\text{Initial total long involvement} - \text{Day 14 total long involvement})}{\text{Initial total lung involvement}} \times 100$$

***2.5.Statistical analysis***

Normality of data was checked with Shapiro-Wilk Test. Independent sample t-test and Mann-Whitney U test (comparison of continuous variables between two groups), Wilcoxon matched-pair signed-rank test (comparison of continuous variables before and after treatment), and $Chi^2$ test (comparing the qualitative data) were used for analysis. The method of analysis was intention-to-treat. The SPSS software version 21.0 (SPSS, Inc., Chicago, IL) was applied for statistical analysis.

## 3.Results

### 3.1.Patients

Sixty subjects were enrolled including FBX (N = 30) and HCQ groups (N = 30) (Figure 1). Six patients (1 patient in FBX group and 5 patients in HCQ group) were excluded, because patients were not interest to continue the treatment (Figure 1). Table 1 shows baseline demographic and clinical characteristics of the 54 patients who were enrolled in the study. The mean age of patients was 57.7 ± 8.4 years, and 59% of the patients were men. Among these patients, the most common symptom was fever, followed by cough and shortness of breath. On admission, fever as temperature ≥37.8 $^{o}$C (66.7%), cough (87%), respiratory rate > 20/min (44.4%), dyspnea (35%), elevated CRP value (94.4%) and lung involvement according to chest CT (100%) were documented in enrolled patients. The WBC counts were 4578 ± 1539 /microL. On admission, lymphopenia (lymphocytes count <1500/microL) was found in 44 (81.5%) of patients and most patients had a moderate pneumonia as

documented by clinical manifestations and CT findings. There were not between-group significant differences in baseline demographic characteristics, laboratory data (e.g., CRP, WBC and lymphocytes counts) and CT scores of lung lesions (Table 1).

**3.2.Oucomes**

The rate of hospitalization, the primary endpoint of the study, was nor different among groups. Six patients (11%, 3 patients in each group) were hospitalized because of developing more severe symptoms. The rate of intensive care unit (ICU) care and also mortality rate was not different between patients received FBX or HCQ. All hospitalized patients were released from hospitals between 1 to 7 days of hospitalization.

Patients were re-evaluated at five days after admission and using FBX or HCQ. Fever, cough and tachypnea significantly mitigated in patients treated with either FBX or HCQ after five days of treatment ($P$<0.01 compared to baseline of each group) (Table 2). It was not observed any significant difference in clinical symptoms after 5 days of treatment between FBX and HCQ groups. Also, the lymphocytes counts significantly increased in both treatment groups. The mean lymphocytes counts were 1308 ± 617 and 1258 ± 498 for FBX and HCQ groups at first days of admission whereas they increased to 1962 ± 478 and 1911 ± 798 after 5 days with FBX and HCQ treatments, respectively. No significant differences were observed between FBX and HCQ in lymphocytes counts. The CRP values dropped in normal range (non-elevated value) in most of patients after receiving FBX or HCQ treatment. FBX and HCQ treatments showed insignificant difference in the percentages of non-elevated CRP values after 5 days of treatments.

Finding of chest CT scans at baseline and day 14 indicated that the percent of lung involvement were 16% and 19.2% in FBX and HCQ groups at admission, while these scores significantly reduced to 7.3% and 8% after 14 days of treatment, respectively, in which the adjusted reduction of lung involvement were 47.4% and 58.3% as compared to the initial CT findings ($P$ = 0.004 and <0.001, respectively).

**4.Discussion**

This open label clinical trial found that the efficacy of FBX and HCQ in treatment of patients with COVID-19 infection is not significantly different in terms of resolution of clinical manifestations and para-clinical abnormalities in outpatients with suspected Covid-19 infection. Six patients including 3 out of 29 (10%) patients in FBX group and 3 out of 25 (12%) patients in HCQ were admitted to hospital because of progressing symptoms, but they did not need ICU admission, a totally 11% of patients needed to be hospitalized. In China, 15-20% of cases required hospitalization, around 15% had severe disease and 5% needed critical care [19]. In Italy, approximately 40% of patients have been hospitalized, whereas nearly 7% admitted to ICU [20]. There is significant variation in the rate of hospitalization of patients with Covid-19 in the world. However, sample size of our clinical trial was smaller and patients with significant comorbidities such as sever cardiovascular and renal diseases were excluded in our trial. Clinical symptoms such as fever, cough and shortness of breath were observed in a large proportion of patients at admission, but these manifestations markedly reduced or resolved (e.g., fever and dyspnea) after 5 days following use of FBX or HCQ. It was not observed any statistically difference in mitigating of clinical symptoms between FBX and HCQ treatments. Low lymphocyte count has been consistently reported in patients with COVID-19 infection (in 80% of cases) and may indicate the severity of disease and serve as a predictor of prognosis [21]. More than half of patients show elevated values of CRP. Patients with severe disease had more prominent laboratory abnormalities than those with non-severe disease [22]. In our study, lymphopenia was observed in 81.5% of patients at onset of admission and significantly increased after 5 days of treatments into normal range. It is shown that both treatments significantly improved lymphocyte counts during 5 days of treatments. Elevated CRP values were observed in the majority of patients [FBX (96.6%) and HCQ (92%)] at onset of admission, while it significantly decreased to non-elevated range in 50% and 40% of patients received FBX and HCQ, respectively. The differences between two groups in terms of changes in CRP after 5 days were not significant. Chest CT images from patients with COVID-19 typically demonstrate bilateral, peripheral ground glass opacities. In China report, of 975 CT scans that were performed at the time of admission, 86.2% revealed abnormal results [22]. In our study, diagnosis was based on clinical symptoms, laboratory findings, history of exposure to a patient with COVID-19 infection and lung CT abnormalities consistent with coronavirus pneumonia at early phase. Due to a high sensitivity of lung CT in detecting lung

involvement and also the importance of initiating the treatment as soon as possible, we included patients according to chest CT findings. The real time Reverse Transcription Polymerase Chain Reaction (rRT-PCR) were not performed in our trial. We believe that this limitation would not affect the validity of our results. The value of high sensitivity chest CT in diagnosis of COVID-19 infection was frequently reported in previous studies. Long *et al,* reported 97.2% sensitivity for CT whereas the sensitivity of initial rRT-PCR was only 83.3%. Considering the false-negative results of rRT-PCR and the relatively long assay time, they suggested that patients with typical CT findings but negative rRT-PCR results should be isolated and a repeated rRT-PCR conducted to avoid misdiagnosis [23]. In our study, all patients showed chest CT abnormalities (100%) at admission, while FBX or HCQ treatments significantly cleared CT abnormalities in 31% and 32% of patients after 14 days of treatments, respectively. All data show that FBX is affective as HCQ in improvement of clinical symptoms and also laboratory and radiographic abnormalities in outpatients with suspected COVID-19 infection. To date, no FDA-approved drug has demonstrated safety and efficacy in randomized controlled trials for patients infected with COVID-19. Several drugs with *in vitro* antiviral activity against SARS-CoV-2 and/or immunomodulatory effects have been suggested to be clinically beneficial in patients with COVID-19. In our protocol, HCQ is prescribed in combination with acetaminophen for controlling fever. However, antiviral drug(s) may be added to HCQ in spite of some challenges regarding the effectiveness or safety of available antiviral medicines for management of patients with COVID-19 disease. Considering these challenges and low severity of disease, we have not prescribed antiviral medicines in our study. Several clinical studies used chloroquine (CQ) or HCQ in treatment of SARS-CoV-2-caused pneumonia in China. The first results of a trial included 100 patients showed the superiority of CQ compared with control group in terms of reduction of exacerbation of pneumonia, duration of symptoms and delay of viral clearance, without severe side effects. This has led to include CQ in the recommendations regarding the prevention and treatment of COVID-19 caused pneumonia. The antiviral and anti-inflammatory activities of CQ may account for its efficacy in treating patients with COVID-19 caused pneumonia [24-26]. In a trial conducted in France, a higher frequency of SARS-CoV-2 clearance was noticed after 6 days of treatment with HCQ alone or HCQ+ azithromycin (AZM) versus the untreated control group (70% vs 12.5%; $P < 0.001$). In that study, PCR results of nasopharyngeal samples and clearing viral nasopharyngeal

carriage of SARS-CoV-2 in COVID-19 patients were evaluated. The clinical symptoms, laboratory tests and lung CT features were reported to be similar in both groups of patients [17]. In other study, Gautret, *et al* conducted an uncontrolled non-comparative observational study in a cohort of 80 mildly infected inpatients treated with a combination of HCQ and AZT over a period of at least three days. A rapid fall of nasopharyngeal viral load tested by qPCR was noted, with 83% negative at Day 7, and 93% at Day 8. Authors concluded that they have provided evidence of a beneficial effect of co-administration of HCQ with AZT in the treatment of COVID-19 and its potential effectiveness in the early stages of contagiousness [27]. To date, despite some promising results associated with efficacy and safety of HCQ in COVID-19, the evidence regarding its effect remains limited [28]. Infrequent and rare side effects include retinal toxicity, cardiac toxicity, QT interval prolongation and agranulocytosis have been reported in patients receiving HCQ or CQ. Life threatening arrhythmias following use of CQ and HCQ appear to be rare but cardiac monitoring is necessary if the drug is being used more extensively [29, 30]. HCQ inhibits IL-6, TNF-α, IL-1β and NF-κB [31-35], and it has immunomodulatory and anti-inflammatory effects [32, 36, 37], which may be beneficial in patients with COVID-19 who inflammatory response and storm cytokine production plays a major role in damaging the lung tissue [37]. There are complex interactions between inflammation and thrombosis, that inflammation is causing a thrombotic tendency. The suspected contribution of thrombotic events to morbidity and mortality in COVID-19 patients, it is recommended to use medicine with anti-inflammatory and antithrombotic properties for prevention or management of thrombosis in COVID-19 [38]. Recently in the recovery trial found that use of dexamethasone was associated with mortality benefit in patients with severe form of COVID-19 infection [39]. NF-κB plays a central role in inflammatory diseases such as rheumatoid arthritis, inflammatory bowel disease, and autoimmunity. NF-κB is activated through microbial products and also pro-inflammatory cytokines, as well as endogenous ligands that function as its trigger during tissue injury, the latter of which may promote inflammation in the absence of infection [40-42]. In addition, viral infections cause NF-κB overexpression, which plays a crucial role in the production of pro-inflammatory cytokine storms and triggers various cellular responses including cell phagocytosis, dendritic cell maturation, chemotaxis and lipopolysaccharide-induced pulmonary inflammation [6, 43, 44]. It seems that downregulation of NF-κB results in the attenuation of inflammatory cytokine signaling and

may be a promising target for lung protection [45]. FBX is in a class of medications called xanthine oxidase (OX) inhibitors leading to decrease in uric acid production. Beside decreasing serum uric acid in gout by FBX, there are well documents demonstrating FBX suppresses pro-inflammatory cytokines such as IL-1β, IL-6 MCP-1 and TNF-α as well as inhibits the oxidative stress and inflammatory responses through NF-κB pathway in animal models [10, 12, 46, 47]. FBX is able to improve lung damage induced by toxic agents through down-regulation of oxidative stress pathway and suppression of inflammatory mediators [8, 16, 48, 49]. To date, there is not any report associated to anti-viral activity of FBX. Xanthine oxidase, which is responsible for the generation of oxygen free radicals, was elevated in serum and lung tissue of mice infected with influenza virus [50-52]. Due to the crucial roles of cytokines and pro-inflammatory mediators in severe acute respiratory syndrome induced by COVID-19, with respect to beneficial effects of FBX in blockading the activation of cytokines and NF-κB pathway, this medicine seems to be an effective drug for the prevention and treatment of lung inflammation in patients with COVID-19 insignificant efficacy with HCQ. However, further studies are needed to find the exact mechanism of FBX in treatment of COVID-19 infection. The adverse effects associated with FBX therapy include nausea, diarrhea, arthralgia, headache, increased hepatic serum enzyme levels, rash and cardiovascular problems. These side effects were not observed in our study, which may be due to the short time consuming of FBX. It is also notable that we excluded patients with cardiovascular and chronic kidney diseases. The limitation of our study was the absence of placebo group. Considering ethical issues, we designed this study without a placebo group due to the life-threatening nature of COVID-19 infection.

## 5.CONCLUSION

Our trial suggests a beneficial effect of administration of FBX in patients with suspected mild-to-moderate COVID-19 infection. The effects of FBX and HCQ was not different in terms of need to hospitalization, improvement in clinical symptoms and CT findings pointing out the lung involvement. FBX may be considered in patients who are not a good candidate of HCQ due to underlying cardiovascular diseases.

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## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

## CONFLICT OF INTEREST STATEMENT

The authors declare no potential conflicts of interest with respect to authorship, and/or publication of this study.

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**Table 1.** Demographic and clinical characteristics of the patients at Baseline

| **Characteristic** | **Total (N = 54 )** | **Febuxostat (N = 29)** | **Hydroxychloroquine (N =25 )** |
|---|---|---|---|
| Age (Mean ± SEM) | 57.7 ± 1.26 | 58 ± 1.47 | 57.3 ± 2.2 |
| Male sex; no (%) | 32 (59.3) | 16 (55.2) | 16 (64) |
| Current smoking; no. (%) | 1 (1.9) | 1 (3.6) | 0 (0) |
| Coexisting conditions | | | |
| Diabetes; no. (%) | 15 (27.8) | 8 (27.6) | 7 (28) |
| Lung disease; no. (%) | 1 (1.9) | 0 (0) | 1 (4) |
| Fever (T> 37.8 °C) | 36 (66.7) | 16 (55.2) | 20 (80) |
| Body temperature; °C | | | |
| Mean ± SEM | 37.7 ± 0.07 | 37.6 ± 0.09 | 37.9 ± 0.09 |
| Respiratory rate | | | |
| Mean ± SEM | 19.7 ± 0.24 | 19.8 ± 0.32 | 19.6 ± 0.37 |
| Respiratory rate ≥20/min; no. (%) | 24 (44.4) | 14 (50) | 10 (40) |
| Cough; no. (%) | 47 (87%) | 27 (93.1) | 20 (80) |
| Dyspnea; no. (%) | 19 (35.2%) | 10 (35) | 9 (36) |
| White Blood Cell count | | | |
| Mean ± SEM | 4578 ± 211 | 4689 ± 321 | 4444 ± 265 |
| Lymphocyte count | | | |
| Mean ± SEM | 1285 ± 76 | 1308 ± 114 | 1258 ± 100 |
| Lymphopenia (< 1500 /microL) | 44 (81.5) | 23 (79.3) | 21 (84) |
| CRP (Elevated value); no. (%) | 51 (94.4) | 28 (96.6) | 23 (92) |

| | | | |
|---|---|---|---|
| Lung CT (%involvement)<br>Mean ± SEM | 17.5 ± 1.35 | 16 ± 1.2 | 19.2 ± 2.6 |

There were not any significant differences between two groups in baseline demographic and clinical characteristics

**Table 2.** Outcomes in the febuxostat and hydroxychloroquine treatments

| **Characteristic** | **Febuxostat (N = 29)** | | | **Hydroxychloroquine (N = 25 )** | | |
|---|---|---|---|---|---|---|
| | Day 1 | Day 5 | P-value (within group) | Day 1 | Day 5 | P-value (within group) |
| Fever (T> 37.8 °C); n (%) | 16 (55.2) | 0 (0) | NA$^{\zeta}$ | 20 (80) | 0 (0) | NA$^{\zeta}$ |
| Body temperature; °C<br>Mean ± SEM | 37.6 ± 0.09 | 37.1 ± 0.27 | 0.001 | 37.9 ± 0.09 | 37 ± 0.23 | < 0.001 |
| Respiratory rate;<br>Mean ± SEM | 19.8 ± 0.32 | 17.3 ± 0.48 | <0.001 | 19.6 ± 0.37 | 17.4 ± 0.48 | 0.001 |
| Respiratory rate ≥20/min; no. (%) | 14 (50) | 2 (6.9) | <0.001 | 10 (40) | 3 (12) | 0.04 |
| Cough; n (%) | 27 (93.1) | 13 (44.8) | < 0.001 | 20(80) | 10 (43.5) | 0.008 |
| Dyspnea; n (%) | 10 (34.5) | 3 (10.7) | 0.07 | 9 (36) | 4 (17.4) | 0.06 |

| | | | | | | |
|---|---|---|---|---|---|---|
| White-cell count; Mean ± SEM | 4689 ± 321 | 6111 ± 1511 | < 0.001 | 4444± 265 | 6130 ± 1421 | 0.001 |
| Lymphocyte count; Mean ± SEM | 1308 ± 114 | 1962 ± 748 | < 0.001 | 1258 ± 100 | 1911 ± 798 | 0.002 |
| Lymphopenia (< 1500/microL) Positive; n (%) | 23 (79.3) | 8 (28.6) | < 0.001 | 21 (84) | 7 (30.4) | < 0.001 |
| CRP (Elevated value); n (%) | 28 (96.6) | 14 (50) | < 0.001 | 23 (92) | 12 (60) | 0.03 |
| Lung CT (% involvement); | | | | | | |
| Mean ± SEM | 16 ±1.2 | 7.3 ± 11.7 | 0.004 | 19.2 ± 2.6 | 8 ±11.8 | < 0.001 |
| Range | 5-25 | 0-50[&] | | 5-50 | 0-50[&] | |
| Reduced lung CT involvement; not adjusted[&]; | | | | | | |
| Mean ± SEM | - 8.4 ±2.4 | | | - 10.8 ±2.3 | | |
| Range | -25 to + 30 [&] | | | -45 to + 10 [&] | | |
| Reduced lung CT involvement; adjusted[&]; | | | | | | |
| Mean ± SEM | 47.4 ± 17 | | | 58.3 ± 13.7 | | |
| Range | -200 to +100 [&] | | | -200 to + 100 [&] | | |
| CT day14 involvement, Negative; n (%) | 9 (31) | | | 8 (32) | | |
| Hospitalization no. (%) | 3 (10.3) | | | 3 (12.5) | | |

&: indicate the Lung CT data on day 14 compared to Day 1; P-value for between groups differences were not significant for any of variables both on day 1 and day 14.

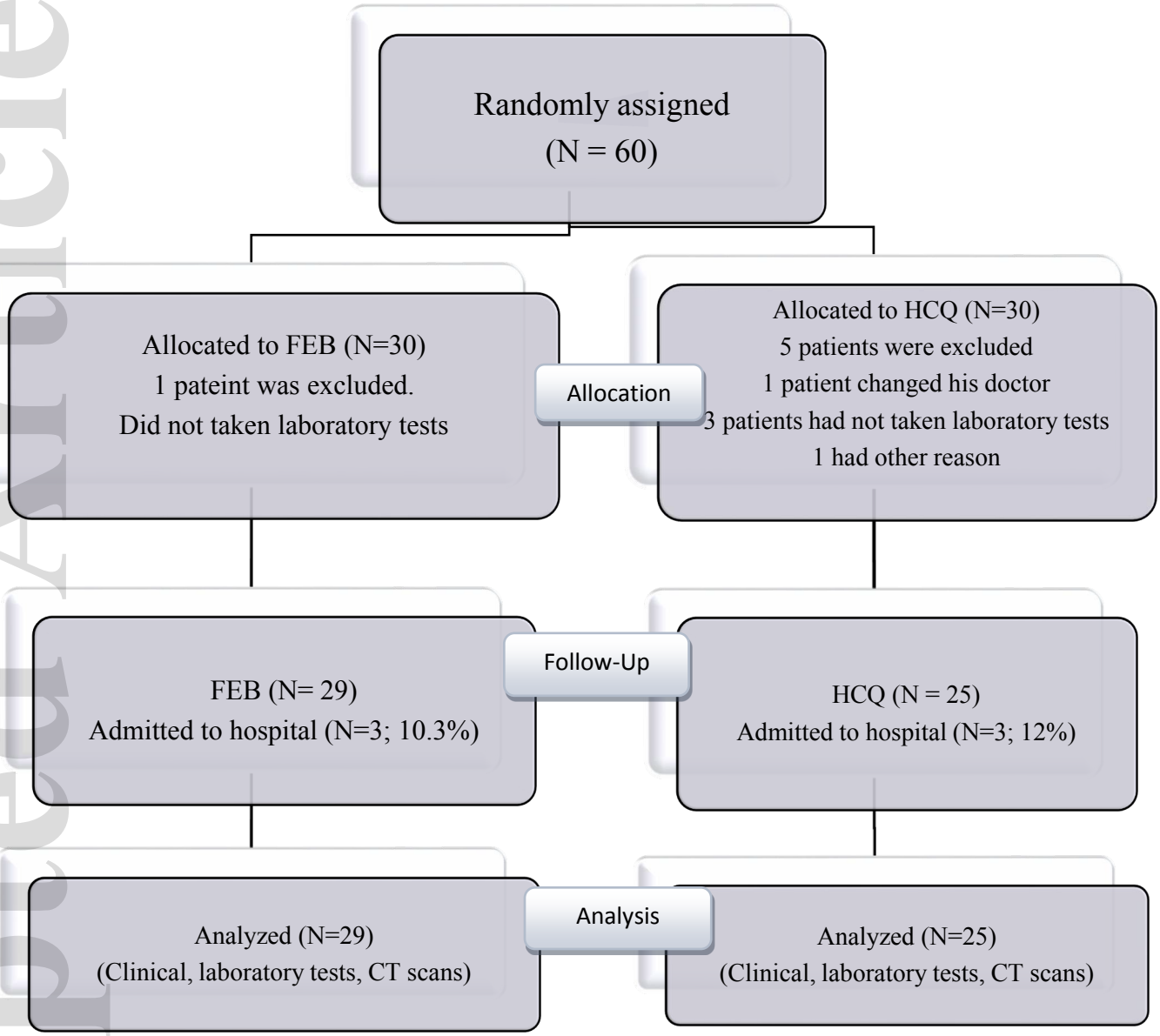


**Figure 1:** CONSORT diagram, including the number of patients who started and continued trial treatment, and stopped.